THE METABOLIC RESPONSE TO EXFOLIATION*

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Patients with extensive exfoliative dermatoses develop many of the stigmata of negative nitrogen balance—edema, hypoalbuminemia, and loss of muscle mass (1, 2, 3). However, the balance data available in the literature demonstrates normal or positive nitrogen balance in these patients (4, 5). Schamberg (4) in 1913 performed extensive balance studies on six psoriatics and concluded that these patients were in positive nitrogen balance. Review of his data suggests that he was dealing with a debilitated patient population during the recovery phase of their illness, a time when they would be expected to be in positive nitrogen balance. A more recent study by Block *et al.* (5) showed that psoriatics were in normal nitrogen balance; however, his patients were exfoliating only small amounts of scale each day.

Since there was a lack of information available concerning the systemic metabolic effects of exfoliating dermatoses, a study was instituted designed to evaluate the metabolic response to exfoliation and to determine whether any existing negative nitrogen balance was related primarily to the dermatologic disease or was merely a manifestation of protein loss through exfoliation. During the course of this study the significance of changes in extrarenal water loss in exfoliating disease became apparent. The magnitude of this loss had been clearly demonstrated by Felsher and Rothman in 1945 (6). The purpose of this report is to present data on nitrogen, potassium and water balance in patients with exfoliating dermatoses and to demonstrate the prognostic and therapeutic significance of such data.

MATERIALS AND METHODS

Patients were admitted to the Mallinckrodt Research Ward of the Massachusetts General Hospital and initial studies were performed to ascertain the existence of any systemic disease other than the presenting dermatologic problem. Patients were ambulatory throughout the period of study with normal ward activity and occupational therapy permitted. No local therapy was used and bathing was not permitted during the time of study. Although no attempt was made to control environmental conditions, the studies were performed during the late winter and early spring, at which time the changes in ambient temperature and humidity on the research ward were minimal. Subjects were studied on a constant diet of calculated composition which contained approximately 25 cal./kg. body weight and 1 gm. of protein/kg. body weight.

Aliquots of each diet used were collected for analysis at the beginning and end of each study period to determine the exact composition and to check on continuous uniformity. A 25% sample of each diet was thoroughly mixed in a Waring blender and made up to 2 litres with distilled water. Urine was collected in 3 day pools in glass bottles and kept under constant refrigeration. Stools were collected in 6 day pools, homogenized in a Waring blender, and made up to volume with distilled water. Nitrogen analyses were done by the Kjeldahl method and potassium was determined with the flame photometer after digestion of stool and diet homogenates (7, 8, 9). Stool water was estimated by weighing stool before and after drying in an oven for 24 hours at 60° C. Creatinine was analyzed by the method of Folin (10).

Throughout the period of study, each patient was dressed in a one piece garment which left only the face exposed (Figure 1). A projecting mask was attached which trapped exfoliated material from the face and yet permitted the patient to eat. Zippered openings were provided so that blood samples could be drawn and the patients could urinate and defecate without removing the uniform. During the night some scales were lost from the face, but these were collected by vacuuming the bed and plastic trough which had been placed around it. At the end of each collection period, the patient was placed in a plastic seamless bag where the garment was removed and turned inside out. Male patients were shaved with an electric razor and all stubble was allowed to fall into the bag. The patient removed all loose scales by brushing with his hands, a method which was found to be superior to using a brush. As the patient stepped out of the bag, he was immediately helped into a fresh garment. The used uniform was agitated and vacuumed and the exfoliated material was weighed and stored at −4° C.

Exfoliated material was prepared for analysis by grinding in a Wiley Mill with #60 mesh to a homogeneous mixture. Nitrogen and potassium

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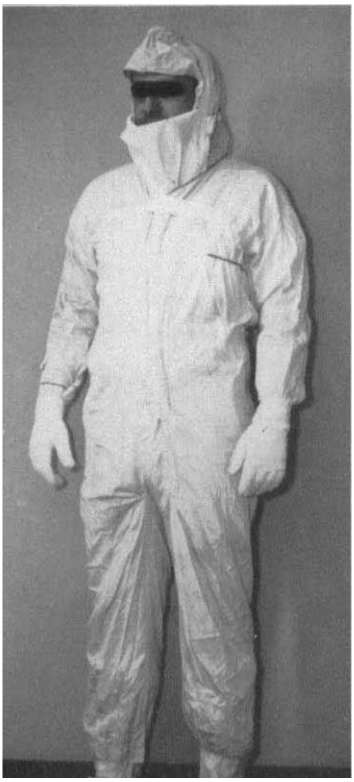

FIG. 1. Garment used for scale collection

concentrations were determined by the methods used for stool and diet homogenates.

Serum albumin turnover was estimated with I^{131} tagged human albumin (Abbott) by the method of Berson (11). During the isotopic study urine collections were divided; one half was frozen and a similar aliquot was preserved with sodium hydroxide, toluene, and carrier iodide. Radioactivity of urine and serum was measured in a well-type scintillation counter.

CASE REPORTS

Case I. (D. M.—MGH #957983) An 84 year old male has had exfoliative dermatitis of unknown etiology for 2 years. Previous therapy consisted of various local ointments and systemic corticosteroids. The present admission followed an exacerbation of his disease. Physical examination revealed diffuse exfoliation and generalized lymphadenopathy. Height was 164 cm. Laboratory data included a hematocrit of 42%, white cell count of 9,500, uric acid of 6.6 mg. per cent, serum albumin of 4.0 gm. per cent, and serum globulin of 2.9 gm. per cent. Urinalysis was normal and on paper electrophoresis an abnormal globulin consistent with an M spot of multiple myeloma was noted. Skin and lymph node biopsies revealed only chronic inflammation. Bone marrow aspiration was normal and no abnormalities were found in x-rays of the chest, GI tract, and skeleton.

The patient was studied on the metabolic ward initially for 15 days and subsequently for 90 days, during which time he underwent a spontaneous remission of his exfoliative dermatitis.

Case II. (L. Z.—MGH #695776) A 48-year-old white female with psoriasis of 31 years duration and severe deforming arthritis of 7 years duration has had multiple admissions for exacerbations of both diseases. Previous episodes of exfoliation were treated with bland local medication. The present admission was precipitated by a sudden exacerbation of psoriasis. Physical examination revealed only abnormalities of skin and joints. There was a universal exfoliative erythroderma and deformity of small and large joints of all extremities. Height was 162 cm. Significant laboratory findings were a hematocrit of 34%, white cell count of 8000, uric acid of 5.5 mg. per cent, serum albumin of 3.3 gm. per cent, globulin of 2.8 gm. per cent. Urinalysis was normal and lupus erythematosus cell preparation and latex fixation tests were negative.

The patient was studied for 63 days during which time she had a spontaneous, but incomplete remission of her exfoliative dermatitis. Because of failure to clear completely, she was given a 9 day course of aminopterin therapy (0.5 mg. per day), following which she had a complete remission for 6 months.

Case III. (M. A.—MGH #280197) A 52-year-old white female with ovarian agenesis has had psoriasis for 32 years. She has had intermittent therapy with estrogen replacement and previous episodes of exfoliation have been treated conservatively. The present admission was necessitated by the gradual development of exfoliative dermatitis. Physical examination revealed a woman of small stature with a webbed neck and universal exfoliative erythroderma. Blood pressure was 200/100 in the arm and 140/100 in the leg. The heart was enlarged 2 cm. beyond the MCL with a grade ii systolic murmur heard over the precordium. The uterus was infantile. Laboratory data included a hematocrit of 39%, white cell count of 10,200, uric acid of 6.1 mgm. per cent, serum albumin of 3.9 gm. per cent, and serum globulin of 1.4 gm. per cent.

The patient was studied for eleven 3-day periods. Following 8 control periods she was treated with 0.5 mg. of aminopterin per day for 7 days. Although marked improvement ensued, the patient insisted on leaving the hospital before the exfoliation was completely arrested.

RESULTS

Nitrogen Balance

Tables IA, I, and II summarize the results of the balance studies in cases I and II. Ac-

TABLES IA AND I

Metabolic balance data on Case I (D. M.)

Period, 3 Days	Average Body Weight, kg	Average Weight of Scales, g	Average Extrarenal Water Loss (Fluid Intake—Urine Output), ml/day	Urine Creatinine, g	Urine Nitrogen, g	Stool Nitrogen, g	Scale Nitrogen, g	Nitrogen Intake, g	Nitrogen Balance (Intake − Output), g	Potassium Output[1], meq	Potassium Intake, meq	Potassium Balance (Intake − Output)[2], meq
1A	64.7	6.7	1479	3.68	30.2	1.2	2.9	39.5	+5.2			
2A	64.9	5.1	1261	3.31	35.0	7.2	2.3		−5.0	291	290	−1
3A	64.0	4.9	1155	3.52	33.0	3.8	2.1		+0.6			
4A	63.7	4.5	1387	3.37	29.9	4.9	2.0		+2.7	304	290	−14
5A	63.5	—	1454	3.72	27.7	6.3	—		—	138	145	+7
1	62.3	6.5	1288	3.12	31.5	2.8	2.7	30.0	−7.0	158	162	+4
2	63.8	5.1	1098	3.49	22.8	2.8	2.1		+2.3			
3	63.3	4.4	911	3.50	26.6	3.4	1.8		−1.8	333	324	−9
4	61.4	6.3	1092	3.69	23.4	3.4	2.6		+0.6			
5	61.2	7.7	1722	3.20	21.1	3.4	3.3		+2.2	355	324	−31
6	61.1	10.7	1604	3.21	23.3	3.4	4.6		−1.3			
7	60.5	9.2	1401	3.49	19.5	1.3	3.9		+5.3	312	324	+12
8	60.3	9.1	1525	3.40	21.9	1.3	3.8		+3.0			
9	60.9	9.6	1356	3.89	22.5	3.8	4.0		−0.3	319	324	+5
10	60.1	10.9	1560	3.50	21.8	3.8	4.2		+0.2			
11	60.1	9.1	1217	3.40	23.4	2.3	3.8		+0.5	338	324	−14
12	60.0	7.1	1122	3.31	23.9	2.3	3.0		+0.8			
13	59.8	7.3	1499	3.18	20.2	1.1	3.1		+5.6	277	327	+50
14	59.9	8.2	1661	3.24	21.4	1.1	4.0		+3.5			
15	60.2	10.1	1593	3.14	20.1	3.9	4.2		+1.8	313	330	+17
16	59.8	10.0	1051	3.02	21.3	3.9	4.2		+0.6			
17	59.5	8.9	1123	3.07	21.4	2.9	3.2		+2.5	356	330	−26
18	59.4	11.6	689	3.27	22.2	2.3	3.2		+2.3			
19	59.3	7.0	1031	3.10	20.7	1.5	3.0	33.0	+7.9	330	360	+30
20	59.0	8.1	876	2.95	19.6	1.5	3.4		+8.5			
21	59.4	8.6	734	3.29	21.4	6.1	3.6		+1.9	324	390	+66
22	58.3	6.8	826	3.13	23.6	6.0	2.9		+0.5			
23	58.2	5.0	702	3.24	22.1	2.6	2.1		+6.2	395	390	−5
24	58.9	5.8	692	3.24	24.4	2.6	2.5		+3.5			
25	58.8	5.2	881	3.31	24.1	2.6	2.2		+4.2	396	390	−6
26	58.5	—	798									
27	57.7	—	908									
28	57.2	2.5	870									
29	58.0	2.5	677									
30	57.9	2.5	599									

[1] Potassium output includes only urine and stool, since the scale loss was found to be less than one per cent of the total output.

[2] Potassium balance is expressed in six day pools.

cording to the criteria of Reifenstein *et al.* (12), the patients are considered to be in balance when the output and intake differ by less than 10%. Patient I was in nitrogen and potassium balance in the periods preceding the elevation in dietary nitrogen in period 19, except for periods 7, 13, and 14. Although the positive balance during these periods is above the significant level, these represent sporadic changes and do not reveal any consistent trend. During periods 19 and 20, the strongly positive balance followed an increase in the protein content of the diet, and the significantly positive results in periods 23, 24, and 25 may represent nitrogen retention

TABLE II

Metabolic balance data on Case II (L. Z.)

Period, 3 Days	Average Body Weight, kg	Average Weight of Scales, g	Average Extrarenal Water Loss (Fluid Intake − Urine Output), ml/day	Urine Creatinine, g	Urine Nitrogen, g	Stool Nitrogen, g	Scale Nitrogen, g	Nitrogen Intake, g	Nitrogen Balance (Intake − Output), g	Potassium Output[1], meq	Potassium Intake, meq	Potassium Balance (Intake − Output)[2], meq
1	52.8	13.7	1235	2.01	24.8	1.5	5.8	28.2	−3.9			
2	51.9	16.6	1425	1.88	24.6	1.5	7.0		−4.9	334	334	0
3	51.5	12.8	1128	1.65	22.2	1.2	5.4		−0.6			
4	50.8	14.3	1140	1.78	22.7	1.2	6.0		−1.7	371	334	−37
5	50.7	14.2	1151	1.66	22.8	2.8	6.0		−3.4			
6	50.5	9.9	1197	1.71	23.8	2.9	4.2		−2.7	371	334	−37
7	51.1	10.1	808	1.69	20.7	2.7	4.3		+0.6			
8	50.4	11.2	695	1.71	21.1	2.7	4.7		−0.3	332	334	+2
9	49.8	9.6	666	1.48	23.6	1.8	4.0		−1.2			
10	49.0	10.0	486	1.70	22.1	1.8	4.2		+0.1	316	334	+18
11	49.8	10.0	666	1.54	18.6	2.8	4.2		+2.6			
12	49.8	5.3	543	1.66	18.5	2.9	2.2		+4.6	344	334	−10
13	48.9	7.4	594	1.55	18.6	2.3	3.1		+4.2			
14	48.9	7.4	501	1.57	20.2	2.4	3.1		+2.5	320	334	+14
15	49.1	8.8	671	1.67	18.9	1.7	3.7		+3.9			
16	49.7	—[3]	771	1.66	19.7	1.7	—		—	344	334	−10
17	49.4	—	656	1.59	23.3	3.8	—		—			
18	49.0	—	724	1.58	20.9	3.9	—		—	305	334	+29
19	48.0	—	423	1.93	18.7	3.6	—		—			
20	47.8	—	346	1.88	19.0	3.6	—		—	283	334	+51
21	48.2	0.6	242	1.72	18.0	2.7	0.2		+7.3	146	167	+21

[1] Potassium output includes only urine and stool, since the scale loss was found to be less than one per cent of the total output.

[2] Potassium balance is expressed in six day pools.

[3] Complete scale collections were not obtained because of necrosis of the skin over pressure areas.

at the higher level of intake in an improving patient. The potassium balance follows the nitrogen balance, except that there is no significant positive balance corresponding to periods 7, 23, 24, and 25.

Figure 2 is a graph of the results of a study of I^{131} albumin metabolism performed in this patient during periods 13 to 18. The half-life of serum albumin was 18 days and the daily rate of degradation was 3.5%, values well within the normal limits (11, 13, 14). Total exchangeable albumin was calculated to be 449 gms., a relatively high value. This may have resulted from an insufficient number of samples obtained on the first day.

In case II there appears to have been a negative nitrogen balance initially during periods 1 through 6 with a reversion to positive balance in periods 12 through 15 and at the end of the study. The potassium data shows the same trends.

From the data in Tables I, II, and III are plotted graphs (Fig. 3, 4, 5) of the daily loss of scales and the daily difference between fluid intake and urinary output (extrarenal water loss). Distinct changes in the extrarenal water loss occurred in all three patients and were correlated with the degree of scaling. In M.A., the stool water was measured and found to average 50 cc per day. Although the stool water was not measured in D.M. and L.Z., the total volume of homogenized stool in each 6 day collection sent for analysis was ¼ to ⅓ the extrarenal water loss. Thus, stool water losses could not account for the degree of extrarenal water loss.

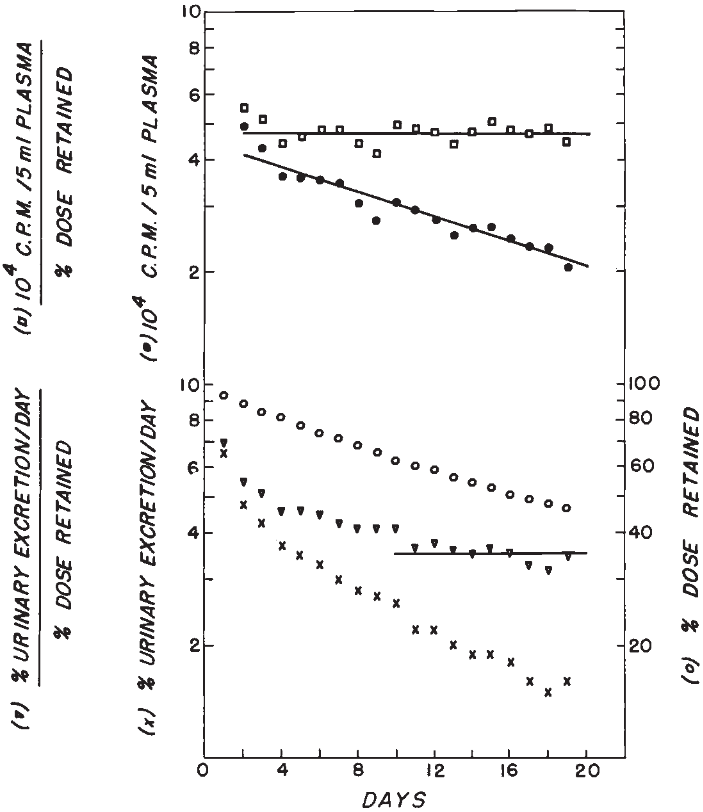

FIG. 2. Graph of I_{131} albumin turnover data on Case I (D. M.)

DISCUSSION

In previous investigations it has been estimated that patients losing 6 to 14 gms. of scale per sq. meter per day will show symptoms and laboratory findings of negative nitrogen balance (15). Despite losing 9.0 gm/day/sq.meter of scale while on a 1 gm/Kg. protein diet, D.M. remained in normal nitrogen balance and showed normal serum albumin turnover. The data for L.Z. shows that when the protein loss by exfoliation reaches 17 gms/day/sq.meter with 1 gm./Kg intake, negative nitrogen balance may result. The absence of edema and normal serum protein values shown by this patient are consistent with the short duration and slight negativity of her nitrogen balance. Evidence of an abnormality of plasma protein turnover may have been demonstrated if I^{131} tagged protein studies had been performed shortly after her admission. Unfortunately such studies were not done on this patient.

Before this study was undertaken, the possibility existed that loss of a special protein such as keratin might result in negative nitrogen balance at low levels of exfoliation. This is not the case. It is the magnitude of the loss which seems to be of importance. One point that has

TABLE III

Balance data on Case III (M. A.)

Period	Average Daily Wt. of Scales, gm.	Average Daily Extrarenal Water Loss
1		1083
2	20.2	933
3	20.2	1041
4	23.7	843
5	20.4	895
6	18.3	690
7	16.0	899
8	10.3	788
9	6.9	834
10	5.5	713
11	5.2	545

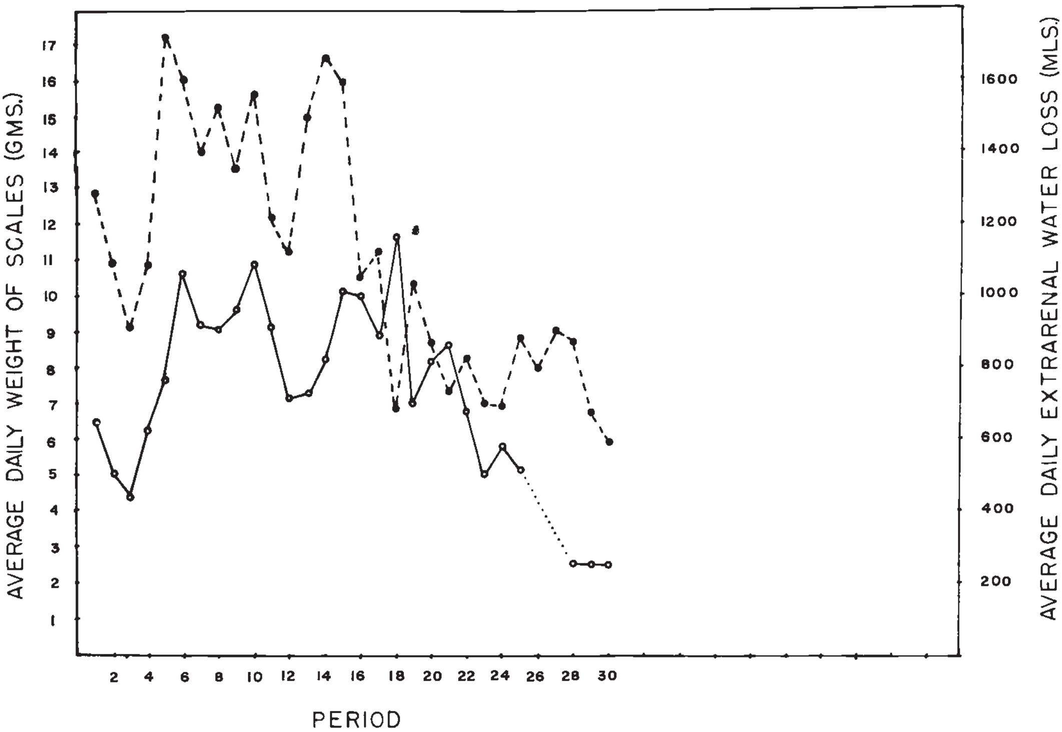

FIG. 3. Graph of scale and extrarenal water losses in Case I (D. M.). —— Scale. ----- Extrarenal water loss.

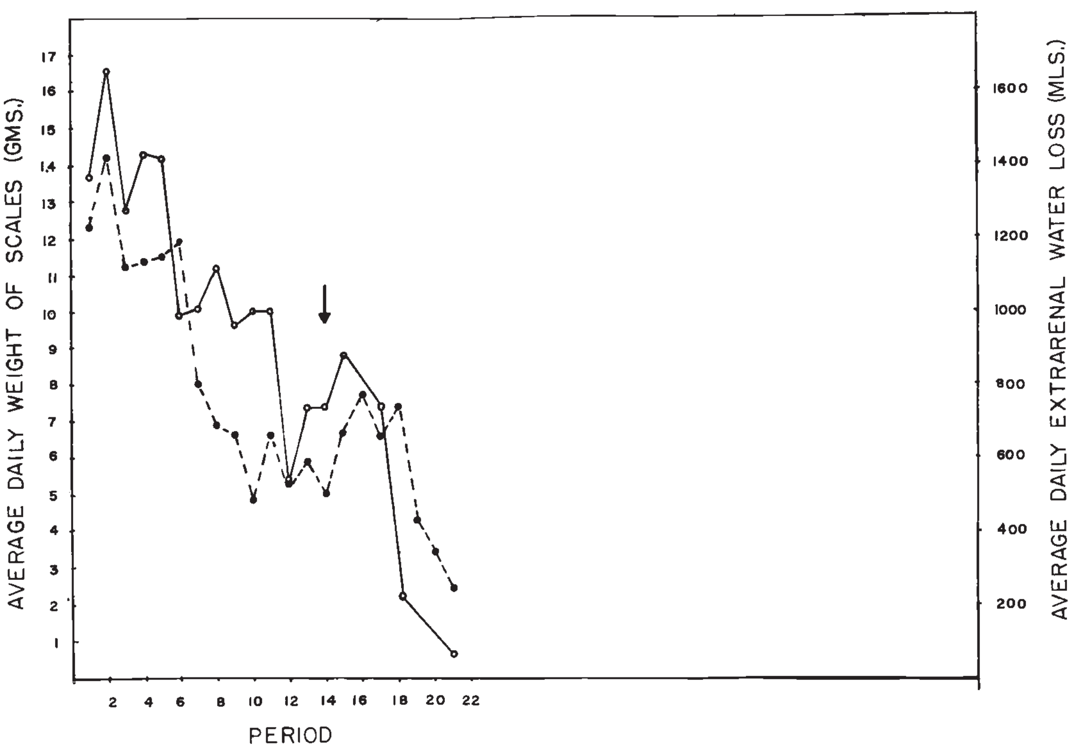

FIG. 4. Graph of scale and extrarenal water losses in Case II (L. Z.). —— Scale. ----- Extrarenal water loss. ↓ Start of 9 day course of aminopterin therapy.

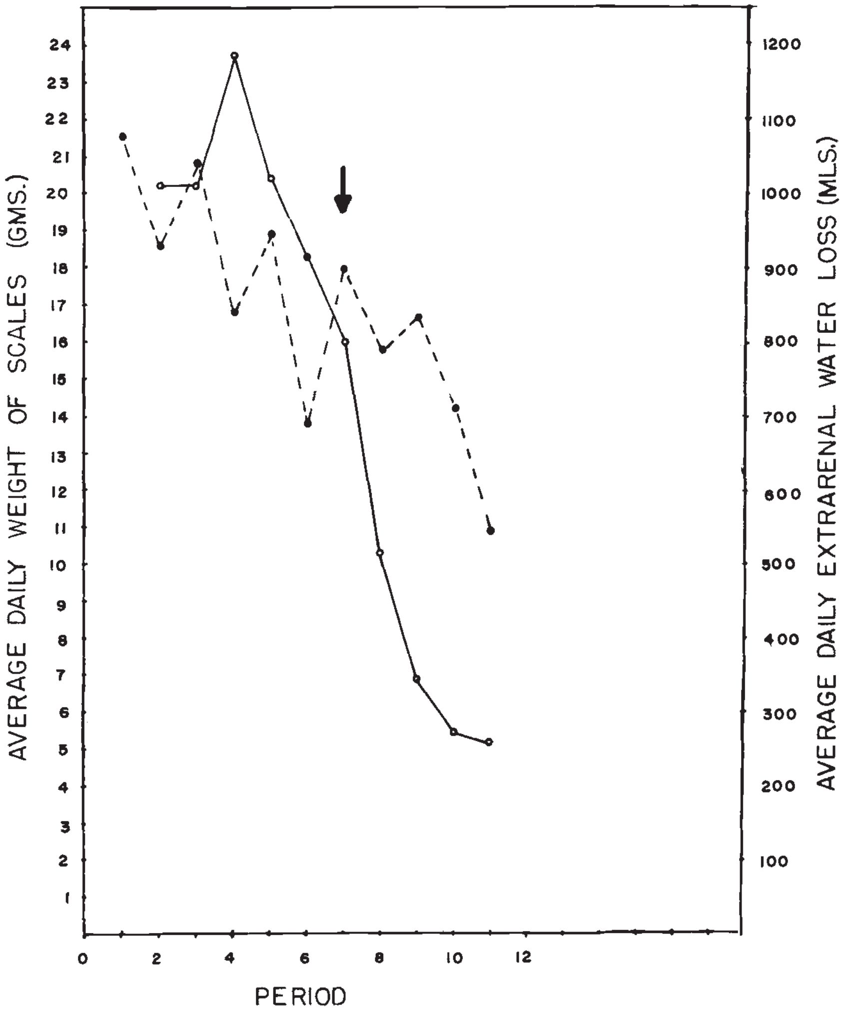

FIG. 5. Graph of scale and extrarenal water losses in Case III (M. A.). —— Scale. ----- Extrarena water loss. ↓ Start of 7 day course of aminopterin therapy.

not been clarified in this study is whether forced feeding of protein in patients with high rates of exfoliation may reverse a negative nitrogen balance. This point will be considered in future studies.

Extrarenal water loss includes losses from the skin, lungs, sweat, and stool. Since there was no significant change in body temperature, respiratory rate, ambient temperature, humidity, or consistency of the stools during these studies, it may be concluded that the changes in extrarenal water loss noted above represent variations in the "insensible" skin loss. The initially increased extrarenal water loss in all 3 patients cannot be attributed to loss of water during the process of keratinization. The production of 20 gms. of scales per day would release only 60 gms. of water as the water content of the epidermis dropped from 70–80% to 10%. Increased transepidermal loss of water through a defective epidermal barrier layer would, however, account for these findings. Electrical measurements of skin conductivity in these patients during their exfoliative stage showed markedly decreased resistance in large areas of involved skin (16). This phenomenon exists only when the barrier is broken (17). The decrease in extrarenal water loss noted in the patients is well correlated with the decrease in exfoliation, thus reflecting a remission of the disease process. In D.M. the remission was entirely spontaneous. In L.Z. and M.A. the decrease in exfoliation and in extrarenal water loss followed a course of aminopterin. During the periods of decreased scaling, all patients still showed considerable skin involvement, and it was difficult to clinically evaluate any gross change in the disease process.

These results, therefore, emphasize the value of measurement of intake and output in patients with exfoliating dermatoses. It is unreliable to depend upon visual estimation of the degree of exfoliation as a measure of the severity and course of the disease. Collection of exfoliated material is a difficult procedure and clinically inapplicable when any local therapy is used. Measurement of the extrarenal water loss, however, yields valuable information with regard to the course and therapeutic response of the patients.

SUMMARY

A reliable method for the collection of scales in patients with exfoliating dermatoses has been described. Using this method, nitrogen, potassium, and water balance studies have been performed. Exfoliation of 9.0 Gm./sq.m./day results in no clinical or laboratory evidence of negative nitrogen balance. Exfoliation may reach 17.0 Gm./sq.m./day without clinical manifestations of protein depletion, although at this level negative nitrogen balance occurred.

There is a correlation between the degree of scaling and the extrarenal water loss. Thus, the measurement of intake and output serves as a clinically applicable method to follow the course and therapeutic response of exfoliative dermatitis.

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